

Synthetic Methods and Reactions; Part 109. Improved Preparation of Aldehydes and Ketones from *N,N*-Dimethylamides and Grignard Reagents¹

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In our continued interest in developing formylation and acylation reactions², we recently reported a convenient formylation procedure using *N*-formylpiperidine³. Either Grignard or organolithium reagents on reaction with *N*-formylpiperidine in ethereal solvents followed by acidic work-up gave excellent yields of the corresponding aldehydes. Our method contrasts with that of Comins and Meyers^{4a,b} who used 2-(*N*-methyl-*N*-

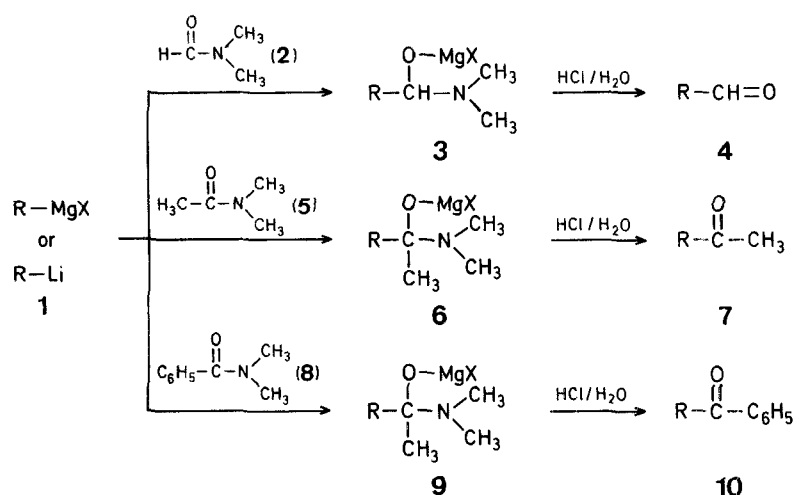
formyl)-aminopyridine as formylating agent. These authors⁴ emphasized that the presence of additional pyridyl ligand is essential for the formation of a chelate ring which would prevent the release of aldehyde under the reaction conditions, thus preventing further reaction. Although *N*-formylpiperidine is a readily available convenient reagent and its use is gaining importance, we have continued our studies evaluating alternative, more inexpensive system such as *N,N*-dimethylamides.

It was Bouveault who in 1903 first reported⁵ the preparation of an aliphatic aldehyde by reacting the corresponding Grignard reagent with *N,N*-dimethylformamide. There is a considerable work in the literature⁶ regarding the reaction of organometallic reagents with *N,N*-dimethyl- and other *N,N*-dialkylamides. However, the reaction has not been proved to be of general utility⁷. Fauvarque and coworkers⁸ in 1972 have reported an improvement of the Bouveault formylation reaction by using a three molar amount of hexamethylphosphoric triamide as a cosolvent. However due to its carcinogenic nature, the use of this reagent is greatly restricted.

We now report that, contrary to earlier reports^{7,8}, Grignard reagents react very smoothly with *N,N*-dimethylformamide, *N,N*-dimethylacetamide, and *N,N*-dimethylbenzamide in usual ethereal solvents to give upon acidic work-up the corresponding carbonyl compounds in good to excellent yields (Table). The reactions must be carried out under mild conditions (0 to 20°C) and with avoidance of excess Grignard reagent. Otherwise secondary reactions, particularly reductions and electron transfer reactions, take place.

In contrast, reaction of alkyl- and aryllithium with *N,N*-dimethylformamide and *N,N*-dimethylacetamide did not give preparatively useful results in our hands, although such reactions have been reported by Evans⁹ and others¹⁰ in the case of alkenyl- and alkynyllithium reagents. This can be attributed to competing one electron transfer processes. *N,N*-Dimethylbenzamide, however, benzoylates organolithium reagents cleanly as, in this case, the tendency for single electron transfer may be decreased.

Comparison of the formylation yields with the those of other existing procedures as shown in the Table demonstrates the utility of the present method. Further, due to the inexpensive



nature of the *N,N*-dialkylamides and their ready availability, the described formylations and acylations should become an attractive alternative to existing methods.

Preparation of Aldehydes and Ketones; General Procedure:

A solution of the corresponding *N,N*-dimethylamide (*N,N*-dimethylformamide, *N,N*-dimethylacetamide, or *N,N*-dimethylbenzamide; 20 mmol) in diethyl ether or tetrahydrofuran (30 ml) is slowly added to the corresponding freshly prepared Grignard reagent (or in the case of *N,N*-dimethylbenzamide also organolithium reagent) (21 mmol) in diethyl ether or tetrahydrofuran (50 ml) at 0°C under nitrogen over a period of 5 min. An instant exothermic reaction takes place with the formation of a sticky white precipitate. The mixture is then brought to room temperature and stirred for 1 h (in case of benzoylation the reaction mixture is refluxed for 4 h). Subsequently, the reaction mixture is carefully quenched with 3 normal hydrochloric acid until the solution becomes acidic. The product is extracted with ether (3 × 50 ml), the

ether layer washed with water (150 ml), aqueous sodium hydrogen carbonate solution (100 ml), and saturated sodium chloride solution (150 ml). After drying of the ether layer with anhydrous magnesium sulfate, the solvent is evaporated to provide the carbonyl product. The carbonyl compound is further purified by recrystallization or distillation. Purity of compounds: ≥98% by I.R., ¹H- and ¹³C-N.M.R. and T.L.C. [silica gel, benzene/hexane (1:1)] analyses.

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Table. Formylation and Acylation of Organometallic Reagents

Reagent 1	Substrate	Solvent	Product type	Yield [%] ^a	m.p. [°C] ^b or b.p. [°C]/torr ^b		Yield [%] from	
					found	reported	Ref. ³	Ref. ^{4a}
	2	ether	4	71 ^c	47–48°/5	70–72°/22 ³	76	—
C ₆ H ₅ –CH ₂ –CH ₂ –MgBr	2	ether	4	81	87°/1	104–105°/13 ^{4a}	—	75
	2	THF	4	59	100°/760	97–100°/740 ³	80	—
	2	ether	4	87	115–116°/0.2	156°/19 ¹¹	94	76
C ₆ H ₅ –CH=CH–MgBr	2	ether	4	68	85°/2	130°/20 ¹¹	86	70
<i>n</i> -C ₅ H ₁₁ –MgBr	2	ether	4	63	131–133°/760	131°/760 ¹¹	—	—
<i>n</i> -C ₄ H ₉ –MgBr	2	ether	4	56	103–104°/760	103°/760 ¹¹	—	—
C ₆ H ₅ –MgBr	2	ether	4	88	57°/13	178–185°/760 ¹²	96	72
	2	ether	4	71	58–60°/20	73–76°/100 ³	72	—
C ₆ H ₅ –CH ₂ –CH ₂ –MgCl	5	ether	7	71	99°/3	115°/13 ¹¹	—	—
<i>n</i> -C ₄ H ₉ –MgI	5	ether	7	61	124–125°/760	127°/760 ¹²	—	—
C ₆ H ₅ –MgBr	5	ether	7	70	73°/10	83–85°/12 ¹¹	—	—
C ₆ H ₅ –CH=CH–MgBr	5	ether	7	79	108°/0.5	151–153°/25 ¹¹	—	—
	8	THF	10	75	89–90°/3.5	121–123°/15 ¹²	—	—
C ₆ H ₅ –Li	8	5:1 ether/THF	10	81	[46–47°]	[49°] ¹¹	—	—
H ₃ C–Li	8	5:1 ether/THF	10	83	73°/10	83–85°/12 ¹¹	—	—
<i>n</i> -C ₄ H ₉ –Li	8	5:1 ether/THF	10	71	90–91°/2.8	105–107°/5 ¹²	—	—

^a Yield of isolated product of ≥98% purity as determined by T.L.C. (silica, 1:1 benzene/hexane), I.R., ¹H-N.M.R., and ¹³C-N.M.R. analysis.

^b Not corrected.

^c Obtained as an *exo/endo* mixture (3:1) starting from *exo*-bromide.

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